

# JOINT SYMBOLIC DYNAMICS ANALYSIS OF HEART RATE AND SYSTOLIC BLOOD PRESSURE INTERACTIONS IN DILATED CARDIOMYOPATHY

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**Abstract-** The dilated cardiomyopathy (DCM) induces important changes in the autonomic control. Measures of heart rate (HR) variability and systolic blood pressure (SP) variability are sensitive to those changes. The interactions between HR and SP are rather complex and strongly non-linear.

We introduced the joint symbolic dynamics (JSD) as a new short-term high resolution non-linear analysis method to investigate the complex interactions between HR and SP.

Continuous non-invasive 30 minutes blood pressure recordings (Portapres) of 25 patients with DCM and 27 healthy controls (CON) were analyzed. HR and SP were extracted from the blood pressure time series on a beat-to-beat basis.

Using the concept of JSD, HR and SP dynamics were transformed into a bivariate symbol vector. Subsequently, this symbol vector was transformed into a word series (words consisting of three successive symbols) and the probability of occurrence of each word type was calculated and compared between both groups. We found significant differences (partly  $p<0.01$ ) in six word types between DCM and CON.

JSD provides an efficient non-linear presentation of HR and SP interactions that offer rather simple physiological interpretations and seems to be particularly suitable for risk stratification in patients with dilated cardiomyopathy.

**Keywords** - Symbolic dynamics, heart rate variability, blood pressure variability

## I. INTRODUCTION

Patients suffering from dilated cardiomyopathy are at risk to die due to sudden cardiac death (SCD). Assessing the autonomic control is crucial for predicting SCD. In this way, the analysis of heart rate variability (HRV) has shown to be of prognostic relevance [1,2]. Newer approaches have been concentrated on multi-modal assessment of biological signals. One dominant impact of HRV comes from the respiratory system. The coupling between HR and respiration has been proven in several studies [3,4]. Besides respiratory modulation, HRV is strongly influenced by blood pressure regulation. To estimate this factor, two main approaches have been established. First, the similarities between HR and SP are analyzed with power spectra density estimation [5]. However, the coherence spectrum presumes stationarity and moreover linearity. Thus, nonlinear interdependencies are neglected. The second approach focuses on special patterns within the HR and SP time series, i.e. sequences of monotonous decreasing SP and in parallel monotonous increasing HR. Those patterns are associated to the baroreceptor reflex and the slope of the HR-SP ratio is used as a measure for the baroreceptor reflex sensitivity [6].

To investigate the short-term interactions between HR and SP more complex, we introduced the joint symbolic dynamics. The concept of symbolic dynamics is based on a coarse-graining of dynamic processes by means of symbols [7]. The time series are translated into an alphabet of symbols. Thus, detailed information are lost but the robust, invariant properties remain and therefore, are easier to interpret.

We hypothesize that JSD provides enhanced information about interactions between HR and SP and therefore, is able to characterize regulatory dysfunctions that are caused by dilated cardiomyopathy.

## II. METHODOLOGY

### A. Data and preprocessing

We compared the JSD of 25 patients suffering from DCM with 27 CON. The CON showed normal values in ECG, exercise ECG and medical history. DCM was confirmed by echocardiography and left ventricular catheterization. The age was comparable in both groups (CON: 50+11 vs. DCM: 50+12).

In all subjects, the continuous blood pressure was recorded over 30 minutes, using a Portapres M2 non-invasive blood pressure monitor (TNO Biomedical Instrumentation, Netherlands) during the late morning hours. Based on Panez' 'volume clamp method' [8] and Wesseling's calibration criteria [9], the device measures the peripheral arterial blood pressure via finger cuff. The accuracy of this method has been investigated in various studies. Although an shift in the absolute pressure values was reported in several cases, the accepted opinion confirms reliable measurement of blood pressure variability [10,11].

The time series of beat-to-beat SP as well as HR were extracted from the Portapres recordings, applying the 'Beatfast' pattern recognition software package from TNO Biomedical Instrumentation. Thereafter, ectopic beats and other disturbances were excluded and interpolated by an adaptive variance estimation algorithm [12].

### B. Joint symbolic dynamics

If  $x$  is the bivariate sample vector of the HR and SP time series (1),  $s^{HR}$  and  $s^{SP}$  are threshold values, then  $w$  represents a bivariate symbol vector (2), gained by transforming  $x$  into a symbol sequence according to (3) and (4).

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$$x = \{[x_n^{HR}, x_n^{SP}]^T\}_{n=0,1,\dots} x \in R \quad (1)$$

$$w = \{[w_n^{HR}, w_n^{SP}]^T\}_{n=0,1,\dots} w \in 0,1 \quad (2)$$

$$w_n^{HR} = \begin{cases} 0 : (x_n^{HR} - x_{n+1}^{HR}) \leq s^{HR} \\ 1 : (x_n^{HR} - x_{n+1}^{HR}) > s^{HR} \end{cases} \quad (3)$$

$$w_n^{SP} = \begin{cases} 0 : (x_n^{SP} - x_{n+1}^{SP}) \leq s^{SP} \\ 1 : (x_n^{SP} - x_{n+1}^{SP}) > s^{SP} \end{cases} \quad (4)$$

In the following the threshold values are set to zero ( $s^{HR}=0$ ,  $s^{SP}=0$ ).

Thus, the bivariate symbol vector  $w$  consists of  $a=4$  symbols. Further,  $w$  is fractionalized to words (bins) of the length  $k$ . The maximum length of words is restricted by the probability of occurrence  $p(w_k)$  of each word type and therefore, indirectly by the amount of measured samples (5).

$$p(w_k) = \frac{N}{a^k} = \frac{2249}{4^3} = 35.14 \quad (5)$$

Precondition for a statistical sufficient quantification is that  $p(w_k)$  should be greater than 30 assuming equal distribution. With 30 min recording time and an estimated mean heart rate of 75 beats / minute  $x$  contains 2250 samples, thus  $w$  has a length of  $N=2249$ . Consequently, the maximum length of words is limited to  $k=3$  spanning a  $8 \times 8$  vector matrix  $W$  from word type  $w_k=[000,000]^T$  to  $w_k=[111,111]^T$  (Fig. 1).

x	79	83	86	78	82	76	73	78	...
	123	127	131	123	121	142	125	132	...
↓									
w	1	1	0	1	0	0	1	...	
	1	1	0	0	1	0	1	...	
↓									
W	HR/SP	000	001	010	011	100	101	110	111
	000								
	001								
	010								
	011								
	100								
	101								
	110								
	111								

Fig. 1. Transformation of vector  $x$  that contains the bivariate heart rate and systolic blood pressure samples, into symbol vector  $w$  and word distribution matrix  $W$ . (x: beat-to-beat heart rate in bpm and beat-to-beat systolic blood pressure in mmHg; w: symbol '1': increasing values, symbol '0': decreasing and equal values; W: row: symbol sequence of heart rate column: symbol sequence of systolic blood pressure.)

These data permit the investigation of the dynamics within four successive heart beats and responding systolic blood pressure values. To compare the word type distribution between data sets of different length the sum of all counted words is normalized to one.

### C. Statistics

To compare the JSD between DCM and CON we calculated group means and standard deviations from all word types and performed a two-tailed t-test. The large number of variables reveals the problem of multiple testing very apparent. According to Bonferroni, a (global) significance ( $p_g$ ) of an observed  $v$ -dimensional parameter space can be guaranteed, if the local p-value ( $p_l$ ) is less than  $p_g$ , divided by the number of variables (6).

$$p_l < \frac{p_g}{v} \quad (6)$$

The global significance level was set at  $p_g=0.05$ , thus  $p_l=0.00078$ . To estimate whether JSD is able to give information about the severity of DCM, we organized a subgroup DCM\* consisting of patients with the lowest ejection fraction.

### III. RESULTS

Fig. 2 and 3 display the three dimensional plots of the probability distribution matrix  $W$  in CON and DCM. Both plots show interactions of HR and SP with deterministic structures rather than stochastic patterns. Significant different word types between DCM and REF are summarized in Tab.1 and Tab.3. There are six word types that fulfill the global significance criterion. The word types  $w_k=[001,000]^T$ ,  $w_k=[011,111]^T$ , and  $w_k=[110,000]^T$  occur significantly less in DCM compared to REF, whereas the word types  $w_k=[000,101]^T$ ,  $w_k=[001,010]^T$ , and  $w_k=[001,101]^T$  occur more frequently in DCM than in REF. The relative differences between the group means range from -54 percent to 226 percent and are displayed in Tab. 2.

Considering the mean of subgroup DCM\*, the trend from CON to DCM continues in five of six word types. This means the word type probabilities  $w_k=[001,000]^T$  and  $w_k=[110,000]^T$  are lower in DCM than in CON and lowest in DCM\*. Conversely, the probabilities of  $w_k=[000,101]^T$ ,  $w_k=[001,010]^T$ , and  $w_k=[001,101]^T$  in DCM are greater than in CON and even greater in DCM\*. The only exception is word type  $w_k=[011,111]^T$ . Here, the group mean in DCM\* is near to DCM (relative difference 5%). The relative differences between DCM and CON as well as between DCM and DCM\* of all words are displayed in Tab. 2.

Word type	CON vs. DCM	CON vs. DCM*	DCM vs. DCM*
[000,101]	225,7	363,5	42,3
[001, 000]	-60,5	-86,2	-65,1
[001,010]	107,0	162,2	26,7
[001,101]	154,2	234,3	31,5
[011,111]	-55,2	-53,2	4,6
[110,000]	-53,5	-65,9	-26,7

Tab. 2. Relative differences between the group means of CON, DCM and DCM\*.

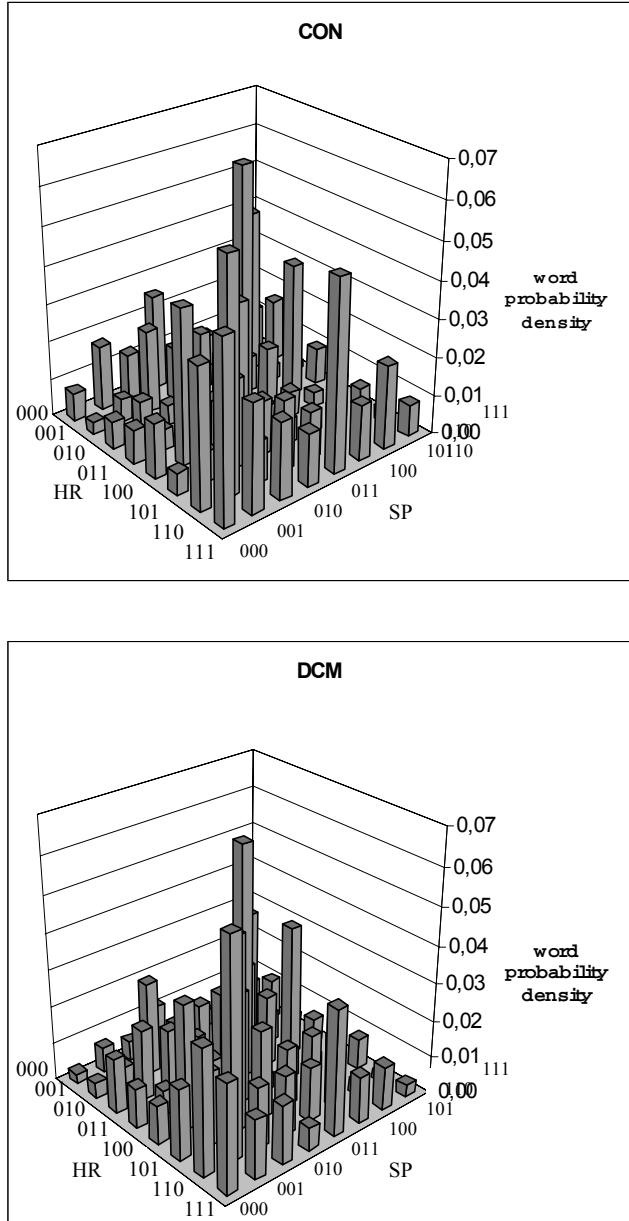


Fig. 2: Word distribution density matrix of CON and DCM. (HR - behavior of three successive interbeat intervals, SP - behavior of three successive systolic blood pressure values)

#### IV. DISCUSSION

In this paper, we introduced a novel approach for the investigation of HR and SP interactions based on JSD. Transforming HR and SP times series into a bivariate symbol vector reveals significant differences in the short-term interactions of both signals between patients with dilated cardiomyopathy and controls.

Word type	CON		DCM		
	wk	mean	sd	mean	sd
[000,101]	0,006	0,004	0,019	0,016	
[001, 000]	0,017	0,012	0,007	0,005	
[001,010]	0,009	0,006	0,019	0,012	
[001,101]	0,008	0,008	0,020	0,011	
[011,111]	0,014	0,009	0,006	0,006	
[110,000]	0,007	0,004	0,003	0,003	

Tab. 1: Significant word types.  
(mean - group mean, sd - standard deviation)

Considering the significant word types in detail, we find pulsus alternans [13] patterns in three cases ( $w_k=[000,101]^T$ ,  $w_k=[001,010]^T$ , and  $w_k=[001,101]^T$ ), i.e. word types containing ‘010’ or ‘101’ patterns. Interestingly, these patterns occur always in SP but not in HR. Comparing the group means of DCM and CON, all these alternans patterns occur significantly more frequent in DCM (Tab. 1). This suggests that pulsus alternans in SP is increased in DCM. The arithmetic average of subgroup DCM\* verifies this assumption (Tab. 2). All three word types occur even more frequently in this group. The data also indicate that there is a relationship between pulsus alternans in SP and HR interactions. Otherwise, all word types featuring alternans patterns in SP should be significant. But that is not the case in the analyzed data. Here, the significant differences in the SP alternans are concentrated on word types with two different patterns in HR, namely ‘000’ and ‘001’. This means that SP alternans occurs significantly more frequent in DCM, if the heart rate drops over three intervals or if the heart rate drops within the first and the second interval or remains constant.

Word type	p <sub>l</sub>	p <sub>g</sub>
[000,101]	0,0004	0,025
[001, 000]	0,0002	0,012
[001,010]	0,0008	0,048
[001,101]	0,0001	0,005
[011,111]	0,0005	0,032
[110,000]	0,0008	0,049

Tab. 3: T-test of significant word types.  
(p<sub>l</sub>-local p-value, p<sub>g</sub>-global p-value)

Besides these three alternans related word types there are significant differences between DCM and CON in the word types  $w_k=[001,000]^T$ ,  $w_k=[011,111]^T$ , and  $w_k=[110,000]^T$ . Focussing on similarities within these word types reveals in all cases monotonous patterns in SP, i.e. '000' or '111' sequences. Contrary to the word types with alternans patterns, these word types occur significantly less often in DCM than in CON (Tab. 1). With the exception of word type  $w_k=[011,111]^T$ , where the group mean in DCM\* is similar to DCM, the subgroup DCM\* continues with this trend and shows more decreased group means than DCM. Not all word types with monotonous patterns in SP differ significantly between DCM and REF, that indicates particular interactions with HR. Surprisingly, baroreceptor reflex patterns considered by the 'sequence method' and the 'dual sequence method' [14] respectively, i.e. word types  $w_k=[000,111]^T$  and  $w_k=[111,000]^T$  do not significantly differ between DCM and CON. This seems to be contrary to previous published findings, where a reduced baroreceptor reflex sensitivity was found in DCM. An explanation for this might be that the sequence methods assess the frequency of baroreceptor reflex activation whereas JSD takes the activation duration into account and does not consider the slope. Probably these different effects compensate each other.

There are two limitations in JSD that should be considered. First, the word length (number of data points) depends exponentially on recording time. Even when using non-invasive monitoring techniques like Portapres, recording times longer than two hours (enables words of length four) are not practicable. However, the analyzed data suggest that even with short sequences of three successive symbols the analysis provides additional and independent information about interactions between HR and SP. The second limitation depends on the number of analyzed data sets. Therefore, JSD should be validated on larger patient groups.

## V. CONCLUSION

JSD provides a new non-linear representation of HR and SP short-term interactions. These interactions are significantly influenced by pathological changes as induced by DCM and are probably dependent on the severity of DCM. Therefore, this method seems to be particularly suitable for risk stratification in patients with dilated cardiomyopathy.

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## REFERENCES

- [1] Stein PK, Kleiger RE: Insights from the study of heart rate variability. *Annu Rev Med* 1999; 50: pp.249-261.
- [2] Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology: Heart rate variability – Standards of Measurement, Physiological Interpretation and Clinical Use. *Circulation* 1996; 93(5): pp.1043-1065.
- [3] Hoyer D, Schmidt K, Bauer R, Zwiener U, Köhler M, Lüthke B, Eiselt M: Nonlinear Analysis of Heart Rate and Respiratory Dynamics. *IEEE Engineering in Medicine and Biology* 1997; Jan/Feb, pp.31-39.
- [4] Schafer C, Rosenblum MG, Kurths J, Abel HH. Heartbeat synchronized with ventilation. *Nature* 1998 Mar 19; 392(6673): pp.239-40.
- [5] Akselrod S, Eliash S, Oz O Cohen S: Hemodynamic regulation in SHR: investigation by spectral analysis. *Am J Physiol.* 1987 Jul, 253(1 Pt 2): H176-83
- [6] Bertinieri G, di Rienzo M, Cavallazzi A, Ferrari AU, Pedotti A, Mancia G: A new approach to analysis of the arterial baroreflex. *J Hypertens Suppl.* 1985; Dec; 3 Suppl 3: pp.79-81.
- [7] Voss A, Kurths J, Kleiner HJ, Witt A, Wessel N, Saparin P, Osterziel KJ, Schurath R, Dietz R: The application of methods of non-linear dynamics for the improved and predictive recognition of patients threatened by sudden cardiac death. *Cardiovascular Research* 1996; 31: pp.419-433
- [8] Penaz J, Voigt A, Teichmann W: Ein Beitrag zur kontinuierlichen indirekten Blutdruckregistrierung. *Z Gesamte Inn Med* 1976 Dec 15; 31(24): pp.1030-3.
- [9] Wesseling KH, de Wit B, van der Joeven GMA, van Goudoever J, Settels JJ: Physiocal, calibrating finger vascular physiology for Finapres. *Homeostasis*. 1995; 36: pp.67-82
- [10] Silke B, McAuley D: Accuracy and precision of blood pressure determination with the Finapres: an overview using re-sampling statistics. *Hum Hypertens* 1998; 12: pp.403-409
- [11] Imholz BP, Wieling W, van-Montfrans GA, Wesseling KH: Fifteen years experience with finger arterial pressure monitoring: assessment of the technology. *Cardiovasc-Res.* 1998 Jun; 38(3): pp.605-16.
- [12] Wessel N, Voss A, Malberg H, Ziehmann C, Voss HU; Schirdewan A, Meyerfeldt U, Kurths J: Nonlinear analysis of complex phenomena in cardiological data. *Herzschriftmachertherapie und Elektrophysiologie* 2000; 11(3): pp.159-173.
- [13] Surawicz B, Fisch C: Cardiac alternans: diverse mechanisms and clinical manifestations. *J Am Coll Cardiol* 1992 Aug; 20(2):pp. 483-99
- [14] Malberg H, Wessel N, Schirdewan A, Osterziel KJ, Voss A: Duale Sequenzmethode zur Analyse der spontanen Baroreflexsensitivität bei Patienten mit dilatativer Kardiomyopathie. *Z Kardiol* 1999; 88: pp.331-337.